RUDOLPH MATAS MEDICAL LIBRARY
TULANE UNIVERSITY
SCHOOL OF MEDICINE
MAR 20 1941

Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION

1790 BROADWAY AT 58TH ST., NEW YORK, N. Y.

DR. JAMES G. CARR, Chicago, *Editor*

DR. GILBERT H. MARQUARDT, Chicago, *Associate Editor*

Vol. X March, 1941 No. 3

THE TREATMENT OF EDEMA

Edema may be defined as the presence of an excessive quantity of serous fluid in the intercellular spaces of the subcutaneous or deeper tissues and in the serous cavities. This fluid was originally in the blood, from which it escaped by passage through the walls of blood vessels. The presence of edema is an indication of some abnormal process, and the aim of medical treatment should be the correction or removal of the cause. Of the many conditions with which edema may be associated only one will be considered in this review, namely, congestive heart failure.

The capillary wall is freely permeable to water and to most of the crystalloids of the blood, and these substances would pass readily into the tissue spaces if there were no opposing factor. But the presence of proteins, chiefly albumin, in the blood plasma exerts a strong counter influence, for these proteins do not pass readily out of the capillaries and by remaining within the lumen they tend to draw fluid into the vessels through the process of osmosis. This force is known as the colloid osmotic pressure of the plasma. It is clear that the direction in which fluid will pass through the capillary wall will depend largely on the balance of these two forces; if the intracapillary blood pressure is higher than the colloid osmotic pressure, fluid will pass out of the vessel, while if the osmotic pressure is higher, fluid will be drawn from the tissue spaces into the blood stream. Edema may result therefore from either or both of two changes: an increase in capillary pressure or a decrease in the amount of protein substances in the blood plasma.

This is only one of the mechanisms concerned in the formation of edema, but is perhaps the most important in patients who have congestive heart failure. Other factors that may be important include a high intake of salt (which increases edema if fluid is available), a high intake of fluid (which increases edema if salt is available), and a warm environment.

Just as in the capillary bed there are two important and opposed physiologic processes involved in the occurrence of edema, so in the kidney there are two opposed processes involved in the formation of urine. According to present beliefs the renal glomerulus is essentially a filter through which enormous quantities of protein-free filtrate pass into the tubules. In the tubules most of this is reabsorbed and the small remaining portion is excreted as urine. It is therefore apparent that the volume of urine may be raised by an increase in glomerular filtration, a decrease in tubular reabsorption, or both.

In congestive heart failure the filtration pressure in the capillaries is increased by the rise in general venous pressure that characterizes heart failure, and probably also by the muscular inactivity that accompanies it. In addition, the capillary wall appears to be more permeable to water and crystalloids, and in many cases the colloid osmotic pressure of the plasma is decreased because some protein passes into the tissue spaces. The hypoproteinemia thus caused is increased at times by the loss of large quantities of albumin in the urine, by anorexia which prevents an adequate protein intake, and unfortunately by a low protein diet that is often deliberately but mistakenly prescribed by the physician.

It must be emphasized that the underlying heart failure should be treated as adequately as possible before specific measures for the removal of edema are employed. Such treatment includes full therapeutic doses of digitalis, complete or partial bed rest, necessary sedatives to ensure adequate sleep, and strict limitation of the fluid and salt intake. These measures alone may result in complete disappearance of edema. There are two important exceptions that should be noted to this general rule. If there is much fluid in one or both pleural cavities, sufficient to interfere with respiration, it should be removed at once by paracentesis. If the edema elsewhere is so marked as to result in danger or extreme discomfort, mercurial diuretics should be administered immediately, without awaiting the possible beneficial effect of digitalization.

DIURETICS

Xanthines. The xanthines, or purines, that are of clinical value consist essentially of theophylline and theobromine and their derivatives. Theophylline may be administered in capsules in doses of 3 to 5 grains (0.2 to 0.325 Gm.) several times a day, but even in small doses is apt to provoke nausea and vomiting within one or two days. Vomiting is less apt to occur, and the total diuretic effect is usually greater, if this drug is administered intermittently for periods of only two or three days at a time. While it is far the most potent of the xanthines, it has fallen into comparative disuse because of its unpleasant side effects, and is now employed chiefly in combination with other salts. Theophylline sodium acetate and theophylline ethylene diamine (aminophylline) are tolerated far better than is theophylline alone, and both preparations are now available in the form of enteric coated tablets. Theophylline with sodium acetate may be given in increasing doses to determine its effectiveness and the tolerance of the patient, but daily quantities of 15 to 30 grains (1 to 2 Gm.) are often well tolerated if administered in three or four equal doses. Aminophylline is less potent, but in doses of 1½ to 3 grains (0.1 to 0.2 Gm.) three or four times a day is sometimes effective in causing the disappearance of slight or moderate edema, or in preventing its reappearance.

Theobromine and its compounds are in general less powerful diuretics than theophylline, but they are usually well tolerated in effective dosage and for this reason are often preferable. Theobromine itself may be given in doses of 5 to 10 grains (0.3 to 0.6 Gm.) thrice daily for a few days unless nausea occurs. Theobromine with sodium salicylate (diuretin) is one of the mildest of all diuretics, is well tolerated by most patients, but must be given in large doses (40 to 60 grains; 2.6 to 4 Gm.). Even these quantities are sometimes ineffective. A more valuable preparation is theobromine calcium salicylate, or theocalcin, which contains about 48% of theobromine. This is a potent diuretic, seldom causes unpleasant symptoms, and may be continued

IMPORTANT ANNOUNCEMENT! The Seventeenth Scientific Meeting of the Association will be held May 30-31, 1941 at Hotel STATLER, instead of Hotel Cleveland as previously stated.

for many days if necessary. The usual effective dose is from three to six tablets a day, each containing 7½ grains (0.5 Gm.).

The precise manner in which the xanthines cause diuresis is not fully known. Some authorities believe that it is chiefly by increasing the filtration through the renal glomerulus, while others ascribe it mainly to diminished reabsorption of water in the renal tubules.

Organic Mercurials. In general there can be no question that the mercurial diuretics are the most potent now available, although an occasional patient may respond better to some other. The best known, salyrgan, contains about 10% of mercury, and is effective only when administered by intramuscular or intravenous injection or in rectal suppositories. The effectiveness of salyrgan is greatly increased if acid-producing salts are administered by mouth for three or four days prior to the injection. Ammonium chloride or ammonium nitrate are those most frequently employed for this purpose, and doses of 45 to 120 grains a day (3 to 8 Gm.) are advocated. The writer has found doses of 60 to 90 grains (4 to 6 Gm.) quite adequate in most cases, and these amounts may be given in the form of enteric coated tablets (each containing 7½ grains or 0.5 Gm.) three or four times a day.

Salyrgan is usually given in a dose of not more than 0.5 to 0.75 cc. at the first injection, in case there should be an idiosyncracy or unusual reaction. Subsequent doses are usually 2 cc., and may be administered every third or fourth day if necessary. If it is to be given at such intervals, the ammonium salt may be continued at the desired level without intermission.

The diuretic effect of this mercurial may sometimes be significantly increased by combining magnesium sulfate with it. A mixture of 2 cc. of salyrgan, 1 to 2 cc. of 1% or 2% procaine hydrochloride, and from 6 to 15 cc. of 50% magnesium sulfate may be injected into the anterior muscles of the thigh, and sometimes results in astonishing diuresis, even after salyrgan intravenously has proved of little value.

There is general agreement that the mercurials owe their diuretic effect largely or wholly to a direct action on the renal tubules, decreasing the reabsorption of water.

In the past decade most mercurials have been modified by the addition of theophylline, inasmuch as studies upon humans and animals have shown conclusively that the combination is far more potent than either alone. The best known of these preparations are mercupurin and salyrgan-theophylline, each of which contains about 5% of theophylline. There is abundant evidence to indicate that the combination of a mercurial with theophylline is the most effective diuretic now available for most patients whose edema is due to heart failure.

Mercurials are available in the form of rectal suppositories which contain about 0.5 Gm. of mercury and a local anesthetic agent to prevent irritation of the rectal mucosa. A cleasing enema should be given first, and it is well to insert the suppository as early in the day as possible, so that the resulting diuresis will not interfere with the night's sleep. Acid-producing salts administered for several days in advance usually increase the potency of the suppository. If rectal irritation does not occur, these preparations may be used with great satisfaction over a long period of time; they have the obvious advantages of self-administration and avoidance of intramuscular or intravenous injections.

Contraindications to the use of the mercurial diuretics are the presence of acute nephritis or of ulcerative colitis. There is little acceptable evidence that the kidneys are injured by the mercury, even after scores or hundreds of injections, and it should be emphasized that the mercurials, especially when combined with theophylline, are safe, highly effective, and usually retain their full potency over long periods of time.

Potassium Salts. It has long been known that in the human being and the experimental animal sodium and potassium salts exert directly opposite effects upon the retention or excretion of fluid by the tissues. The greater the intake of potassium, the greater will be the excretion of water; conversely, a high intake of sodium will result in greater retention of water. Potassium salts have been found highly effective diuretics in many cases of congestive heart failure, and not infrequently prove more satisfactory than any other because they can be administered by mouth without discomfort, and may be continued over long periods of time without loss of effectiveness. The salt most frequently employed for this purpose is potassium chloride, but the nitrate appears to be just as satisfactory. Large doses are necessary for therapeutic effects, the range being in general from 5 to 8 grams a day (Grs. 60 to 120). The writer has found a dose of 5 grams (Grs. 75) a day sufficiently large for most patients, although some have advocated daily amounts larger than this. The salt should be administered in the form of enteric coated tablets three or four times a day. Sodium chloride must be eliminated from the diet as completely as possible, since the objective is to replace sodium by potassium. If a saltless diet proves unpalatable, crystalline potassium chloride may be sprinkled on the food as freely as desired.

The exact mechanism of the increased fluid excretion following the administration of potassium salts is not fully known.

Urea. Urea has been in fairly general use as a diuretic agent in congestive heart failure for nearly twenty years. It must be given in large doses, usually from 30 to 60 grams (Grs. 450 to 900) a day; such doses, if tolerated, may be continued for months or years without harmful effects and with no decrease in diuretic potency. The only serious disadvantage of the drug is its extremely unpleasant taste, which is only partially disguised by the vehicles commonly employed. Grapefruit juice, cranberry juice, tomato juice, and syrup of acacia are especially recommended as vehicles, but even with these it may prove necessary to omit the medication for a few days at intervals in order to prevent nausea and vomiting.

It is less apt to cause distress if given very cold and immediately before or after a meal. A forty per cent solution is satisfactory, and it may be wise to dissolve the urea directly in the selected vehicle, rather than to make an aqueous solution which must then be disguised by the addition of other liquids.

Urea is rapidly excreted by the kidney and carries with it large quantities of water; this mechanical diuresis is aided by diminished reabsorption in the renal tubules. The only important precaution that should be observed in its use is to make sure that it is being excreted. The blood nonprotein nitrogen should be determined after a few days of administration; if it has not risen, urea may be continued safely.

Bismuth. Bismuth sodium tartrate has been found to exert an excellent and prolonged diuretic action in some cases of congestive heart failure, but has not been widely accepted, probably because of the more spectacular action of the mercurials in most cases. Bismuth is administered by intramuscular injection in doses of 0.030 Gm. (Gr. ½), and may lead to diuresis that persists for from four to eighteen days; toxic effects are practically unknown. Because of its prolonged effect, it may prove to be extremely valuable in some cases. The mechanism of its diuretic action has not been fully or satisfactorily described; the statement that it is due to a general action on the tissues, resulting in mobilization of chlorides and water, must be accepted with caution.

H. M. Marvin, M.D.
New Haven, Conn.